Interaction of Grapefruit Juice and Calcium Channel Blockers

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Drug–drug interactions are commonly recognized occurrences in the hypertensive population. Drug–nutrient interactions, however, are less well appreciated. The grapefruit juice–calcium channel blocker interaction is one that has been known since 1989. The basis for this interaction has been diligently explored and appears to relate to both flavanoid and nonflavanoid components of grapefruit juice interfering with enterocyte CYP3A4 activity. In the process, presystemic clearance of susceptible drugs decreases and bioavailability increases. A number of calcium channel blockers are prone to this interaction, with the most prominent interaction occurring with felodipine. The calcium channel blocker and grapefruit juice interaction should be incorporated into the knowledge base of rational therapeutics for the prescribing physician. Am J Hypertens 2006;19:768–773 © 2006 American Journal of Hypertension, Ltd.

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In 1989, it was noted that co-administration of the calcium antagonist felodipine with usual doses of commercially available grapefruit juice substantially decreased the pre-systemic clearance of felodipine. This interaction substantially increased the systemic exposure to felodipine and by this amplified its pharmacodynamic effects. This interaction was discovered by coincidence in the course of an ethanol–drug interaction study in which grapefruit juice was used to mask the taste of the ethanol vehicle. This singular observation has fueled a large volume of grapefruit juice–drug interaction research, with in excess of 225 publications involving more than 25 drugs appearing in the scientific literature. This literature has been extensively reviewed, and the reader is directed to several of these reviews for additional information.

The emphasis in this review will be on the interaction between grapefruit juice and calcium channel blockers (CCB).

Several findings point to grapefruit juice having a principal effect on the intestinal CYP system with a minor effect at the hepatic level. First, medications interacting with grapefruit juice typically are subject to metabolism by the enterocyte CYP3A4 enzyme system. Only the CYP3A isoforms localized to mucosal cells of the small intestine are inhibited by grapefruit juice. Hepatic CYP3A is at best moderately affected by grapefruit juice administration and only with its chronic administration. Second, grapefruit juice increases the area under the plasma concentration time curve, a calculable measure of whole-body medication exposure, with minimal if any change in drug half-life. An interaction involving hepatic CYP3A would be expected to influence drug half-life. Third, in standard dose amounts, grapefruit juice has no effect on the pharmacokinetics of these medications when they are intravenously administered.

Action of Grapefruit Juice on Intestinal CYP Enzymes

The effect of some CYP3A4 inhibitors dissipates with repeated administration, because they produce a time-dependent induction of CYP3A4 via up-regulation of CYP3A messenger RNA and protein, which appears not to be the case with grapefruit juice. Grapefruit juice appears to reduce CYP3A4 activity by both reversible (competitive or noncompetitive) and irreversible (mechanism-based or suicide inhibition) mechanisms as well as through a true loss of CYP3A4. The latter mechanism was first detected when it was observed that recurrent ingestion of grapefruit juice selectively decreased enterocyte expression (obtained by small bowel biopsy) of both CYP3A4 and CYP3A5, thereby increasing drug bioavailability. This effect was selective in that concentrations of CYP1A1 and CYP2D6 did not fall. Moreover, this phenomenon was reproducible when human cell lines modified to express
CYP3A4 were exposed to grapefruit juice. The failure of messenger RNA expression to decrease with grapefruit juice would suggest that this process is not transcriptionally regulated. The mechanism of the decrease in CYP3A4 protein likely represents either accelerated protein degradation or reduced messenger RNA translation.

It is not unreasonable to presume that one or more components of grapefruit juice degrade intestinal CYP3A4 enzyme by way of irreversible “suicide” inhibition. Such a hypothesis explains the rapid and sustained onset of CYP3A4 inhibition upon exposure to grapefruit juice. For example, upon ingestion of grapefruit juice intestinal CYP3A4 concentration is reduced by 47% within 4 h, and the bioavailability-enhancing effect of ingested grapefruit juice is sustained for at least 24 h. Complete recovery from the grapefruit juice effect may take up to 72 h after the last exposure with a recovery half-life from enteric CYP3A4 inhibition of approximately 24 h. Such a recovery pattern is consistent with the time sequence of enzyme regeneration after irreversible (mechanism-based) inhibition.

**Interindividual Variability in the Effect of Grapefruit Juice**

The expression of the CYP3A4 enzyme shows striking interindividual variability in both the liver and intestine with as much as an eightfold difference found in its intestinal content. Higher concentrations of CYP3A4 in the intestine, as logic would suggest, correlate with greater first-pass metabolism and lower attainable drug levels for felodipine. Ingestion of grapefruit juice reduces enteric CYP3A4 levels similarly in all subjects irrespective of the tissue CYP3A4 concentrations before ingestion. However, patients with the highest intestinal CYP3A4 concentrations will exhibit the greatest effects from grapefruit juice; a finding that is apparent upon scrutiny of felodipine bioavailability data. Alternatively, felodipine-treated patients with very low CYP3A4 activity should experience a lesser effect on bioavailability from grapefruit juice.

**P-Glycoprotein, Organic Anion Transporting Polypeptide, and Grapefruit Juice**

Given the overlap in substrate specificity between p-glycoprotein, organic anion transporting polypeptide, and CYP 3A4, grapefruit juice might be expected to interact also with these transporter systems. In fact, in vitro data in intestinal cell monolayer experiments suggest that grapefruit juice activates p-glycoprotein and inhibits multiple oat polypeptides. If relevant effects on p-glycoprotein or oat polypeptides were to be present in vivo, drug bioavailability would be expected to be reduced, thereby partially counteracting the increased bioavailability that arises from inhibition of enterocyte CYP3A4. This concept is supported by the observation that some drugs displaying a reduced grapefruit juice effect are also known substrates for p-glycoprotein. However, current information on the in vivo effect of grapefruit juice on CYP3A4, p-glycoprotein, and oat polypeptides is insufficient to make a qualified statement concerning their mutual interactive effect on bioavailability.

**Active Constituents of Grapefruit Juice**

Soon after the initial report of the grapefruit juice–felodipine interaction, it was shown that other citrus fruit products such as orange juice reconstituted with half the recommended water. Most of the subsequent studies evaluating pharmacokinetic interactions between drugs and grapefruit juice have been performed using one 200-mL glass of juice, as CYP3A4 is substantially inhibited after ingestion of a single glass of grapefruit juice. For example, one glass of regular-strength grapefruit juice is comparable to two to three glasses of double-strength juice in how the pharmacokinetics of felodipine are influenced. Daily ingestion of grapefruit juice over several weeks may slightly attenuate the effect of the juice, because 24 h after ingestion of a glass of grapefruit juice a 30% residual effect exists. Consumption of grapefruit juice in the order of six to eight glasses per day is required if hepatic CYP3A4 is to be inhibited. The lag phase for the effect from grapefruit juice is an additional consideration with this interaction. Rogers et al showed that the daily consumption of a glass of regular-strength grapefruit juice has a minimal effect on plasma concentrations of the 3-hydroxy-3-methylglutaric acid (HMG-CoA) reductase inhibitor lovastatin (approximately 30% to 40% increase) taken approximately 12 h later; however, the length of a lag phase effect for grapefruit juice is likely to be compound specific and highly individualized.
CYP3A25,29 and CYP1A230 isozymes the in vivo demonstration of the same is less striking. Studies of other flavanoids have yielded similar results, that is, strong in vitro inhibition and at best modest in vivo inhibition of the CYP3A system.30–32

Among different strains of grapefruit juice (white or pink), origin (United States, Australia, or Israel), packages (in glass, paper, plastic, or metal containers), and ways of processing (reconstituted, straight, or containing 10% pulp), furanocoumarin compositions appear to be qualitatively similar.33 Among the furanocoumarins, 6′, 7′ dihydroxybergamottin and its parent compound bergamottin are particularly prominent inhibitors of CYP3A4.28,31 These two compounds are the furanocoumarins found in the highest concentration in fresh grapefruit and are present in the low micromolar range.

The substances 6′, 7′ dihydroxybergamottin and bergamottin, either individually or collectively, are not solely responsible for the CYP3A4 inhibitory activity of grapefruit juice as is evident from two experimental findings. First, when specific furanocoumarins are added to grapefruit juice, the level of CYP3A4 inhibition reached is not as significant as that seen with the weakest grapefruit juice studied.33 Second, the furanocoumarin bergamottin (but not 6′, 7′ dihydroxybergamottin) is found in significant quantities in lime juice. However, despite an ample quantity of bergamottin in lime juice its CYP3A4 inhibitory potential is less than that of grapefruit juice.34,35

Thus, the clinical drug interaction between grapefruit juice and CYP3A4 may depend on the net effect of all furanocoumarins and possibly other substances, in grapefruit juice. To this end, many of the furanocoumarin constituents of grapefruit juice are present in a mixture of chiral isomers that vary markedly in proportion and concentration, depending on the maturity of the fruit and the method of juice extraction and purification.13,36 Finally, furanocoumarins are present in similar quantities in grapefruit juice, lime juice, and grapefruit segments and to a lesser degree in peel extract, suggesting that any therapeutic concern for a drug interaction with commercial grapefruit juice should now be extended to whole fruit and perhaps confectioneries produced from grapefruit peel.37

### Calcium Channel Blockers

The 1, 4 dihydropyridine CCB are lipid-soluble drugs metabolized by CYP3A4. The observation that felodipine1,2 interacted with grapefruit juice served as the impetus for the study of most other CCB as to their potential for interacting with grapefruit juice10,12,14,22,26,37 (Table 1).

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**Table 1.** Grapefruit juice and calcium channel blocker interactions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Reference</th>
<th>Grapefruit juice</th>
<th>Compound</th>
<th>Interaction</th>
<th>Severity/onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amlodipine</td>
<td>39</td>
<td>250 mL</td>
<td>5 mg, single-dose 120 mg IR* single-dose</td>
<td>C&lt;sub&gt;max&lt;/sub&gt; ↑ 15% AUC ↑ 16%</td>
<td>Minor/delayed</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>50,53</td>
<td>250 mL</td>
<td>Several single and multiple studies</td>
<td>C&lt;sub&gt;max&lt;/sub&gt; ↑ 22% ± 37% AUC ↑ 20% ± 25%</td>
<td>Minor/delayed</td>
</tr>
<tr>
<td>Felodipine</td>
<td>1,2,10,14,21,37,41</td>
<td>250 mL single-strength; peeled grapefruit segments; intact grapefruit</td>
<td>Bioavailability can ↑ by two to three fold with similar size hemodynamic changes</td>
<td>Moderate/rapid</td>
<td></td>
</tr>
<tr>
<td>Isradipine</td>
<td></td>
<td>300 mL concentrated grapefruit juice</td>
<td>40 mg, single-dose</td>
<td>Not studied AUC ↑ 43% ± 3.4% for [+,-] nicardipine and ↑ 91% ± 6.4% for [-] nicardipine</td>
<td>Unavailable Moderate/rapid</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>44</td>
<td></td>
<td></td>
<td>C&lt;sub&gt;max&lt;/sub&gt; ↑ 40%</td>
<td>Minor/delayed</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>38,48</td>
<td>200 g of grapefruit pulp</td>
<td>20 mg, single-dose</td>
<td>AUC ↑ 30% C&lt;sub&gt;max&lt;/sub&gt; ↑ 24%</td>
<td>Moderate/rapid</td>
</tr>
<tr>
<td>Nimodipine</td>
<td>45</td>
<td>250 mL (751 mg naringin/L)</td>
<td>30 mg, single-dose</td>
<td>C&lt;sub&gt;max&lt;/sub&gt; ↑ 406% ± 73% AUC ↑ 198% ± 46%</td>
<td>Moderate/rapid</td>
</tr>
<tr>
<td>Nisoldipine</td>
<td>42,43</td>
<td>250 mL single-strength</td>
<td>20 mg, single-dose</td>
<td>AUC ↑ 99% C&lt;sub&gt;max&lt;/sub&gt; ↑ 106%</td>
<td>Moderate/rapid</td>
</tr>
<tr>
<td>Nitrendipine</td>
<td>46</td>
<td>150 mL at −15, 10, −1/4, +5, and +10 h 200 mL, normal strength</td>
<td>20-mg, single-dose 60 to 240-mg immediate release from twice daily</td>
<td>No significant Δ in C&lt;sub&gt;max&lt;/sub&gt; or AUC Some interindividual variability</td>
<td>Minor/delayed</td>
</tr>
<tr>
<td>Verapamil</td>
<td>49,51</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Immediate release.
The degree to which the intestinal CYP system metabolizes each of the members of the CCB class varies considerably and hence the varying effect on absolute bioavailability. Grapefruit juice has the greatest effect on those CCB with the lowest oral bioavailability. One glass of grapefruit juice more than doubles the bioavailability of standard and extended-release felodipine, although with considerable interindividual variability (Fig. 1).

Many studies have shown an enhanced blood pressure reduction, a rise in heart rate, and an increase in vasodilatory effects when felodipine is taken together with grapefruit juice. Other dihydropyridines exhibiting the interaction to a similar extent are nisoldipine and nicardipine. A lesser but still significant interaction has been observed with nimodipine and nitrendipine, which have shown a 50% and 100% increase in bioavailability when given together with grapefruit juice. Amloidipine and nifedipine have better inherent bioavailability and hence are less effected by grapefruit juice. However, studies still show a 20% to 30% increase in the blood levels of these CCB in the setting of grapefruit juice ingestion but much less in the way of altered hemodynamic responses or concentration-related adverse effects. Although metabolized in vivo by CYP3A4, the nondihydropyridine CCB diltiazem and verapamil do not have their ability to the hypertensive population. The patient population studied is an important consideration in assessing a grapefruit juice and CCB drug–drug interaction in that hypertensive patient’s typically experience more prominent drug concentration-dependent CCB effects.

Patients receiving an established CCB dose, in whom an unexpected blood pressure response or vasodilator side effect is noted, should be questioned with regard to their intake of grapefruit juice. The question also comes up as to whether this interaction occurs with other types of citrus fruit. Seville oranges contain 6’-dihydroxybergamottin and bergapten, which can prompt the same CCB interaction, observed with grapefruit juice. Seville oranges are commonly used in marmalade production. To date, studies have not been conducted with finished marmalade products to establish the potential for interaction with CCB. Hybrids of grapefruits and mandarin oranges, such as tangelos, have not been directly studied for their interactive potential. Because they are genetically derived from grapefruits they could conceivably have the same potential for a drug–drug interaction.

In conclusion, data from epidemiologic studies reveal that approximately 1% to 2% of the population in the United States consumes at least one glass of regular-strength grapefruit juice per day. This level of intake makes this a pertinent consideration in hypertensive individuals in the U.S., many of whom are receiving CCB therapy. Moreover, grapefruit juice inhibition of oral clearance of CYP 3A4 drug substrates needs to be considered in the broader context of food–drug, nutrient–drug, and environment–drug interactions. Such interactions commonly receive initial wide medical and public acclaim, followed either by incorporation into the knowledge base of rational therapeutics or by a drift into obscurity as a forgotten and perhaps inconsequential annotation. The former applies in this case. A number of regulatory agencies have now addressed the potential for grapefruit
juice to interact with a range of medications. For example, Health Canada issued an advisory alert in June 2002 warning the public not to take certain drugs with grapefruit juice. In July 2002, the American Society of Clinical Pharmacology and Therapeutics in conjunction with the Food and Drug Administration sponsored a drug interaction conference in which the issue of grapefruit juice was prominently discussed. However, despite the importance of this nutrient–drug interaction, package inserts for many of the CCB (particularly in the United Kingdom and Japan) often fail to include the necessary quantitative information for clinical decision making. Thus, the clinician is often called upon to have a working knowledge of which antihypertensive medications are most likely to be influenced by intake of grapefruit juice.

References


